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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,471	09/01/2006	Elliot Ehrich	2685.3002 US	4421

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EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1614	

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10/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,471	EHRICH ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10-16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10-16 and 18-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/06/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' preliminary amendment, filed 09/05/2007, canceling Claims 3, 9, and 17, is acknowledged.

2. Applicants' preliminary amendment, filed 09/22/2005, amending the Specification, is acknowledged; however, Applicants' disclosure that PCT/US2003/27618 claims the benefit of six U.S. Provisional Applications is incorrect. PCT/US2003/27618 is a CIP of U.S. Patent Application 10/392,333, and does not claim benefit to the Provisional Applications. Therefore, Applicants are not entitled to benefit of priority from the cited Provisional Applications.

3. Applicants' Information Disclosure Statement, filed 12/06/2005, is acknowledged and has been reviewed.

4. Claims 1, 2, 4-8, 10-16, and 18-28 are pending.

5. Claims 1, 2, 4-8, 10-16, and 18-28 are under consideration.

Specification

6. The disclosure is objected to because the data presented in Figure 3 do not correspond to its description in the "Brief Description of the Drawings" section of the Specification (page 2) or in the "AIR Trospium Chloride Formulations Compared to Aqueous TrC1 at Equal Doses (1 mcg)" section of the Specification (page 15).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5 and 11-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "trospium **hydrochloride**" (emphasis added). There is insufficient antecedent basis for this limitation in Claim 1, from which Claim 5 depends.

Claim 8 recites the limitation that the composition of Claim 1 "comprises a dry particulate formulation of trospium characterized by a **fine particle fraction** of at least 50%" (emphasis added). The claim fails to disclose the aerodynamic diameter of the particles which comprise at least 50% (by mass) of the composition. Therefore, any particle size will satisfy the limitation of this claim.

The term "less than" in Claims 11, 12, and 15 renders the claims indefinite because it does not adequately define the scope of the claims (i.e., no lower limit is set). For example, Claim 15 is drawn to the formulation of Claim 14, wherein said formulation contains less than 10% by weight of trospium. Since no lower limit is set, the formulation can have 0% trospium.

The term "at least" in Claim 14 renders the claim indefinite because it does not adequately define the scope of the claims (i.e., no upper limit is set).

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 1, 2, 6-8, 10-13, 15, 22-24, and 26-28 rejected under 35 U.S.C. 102(a) as being anticipated by Basu et al. (WO/2003/079885).

Basu et al. teach *inter alia* sustained release dry powder (particle) formulations of therapeutic agents, in combination with leucine and a phospholipid) for their therapeutic, prophylactic or diagnostic action in the pulmonary system (*see* page 9, lines 9-14). The therapeutic agents can be administered by dry powder inhalers (*see* page 11, last paragraph). The therapeutic agents include the anticholinergic drug, trospium, and the beta-2 agonist drug, formoterol (*see* page 9, lines 15-20). Basu et al. also teach the combination of two classes of drugs, including trospium combined with formoterol (*see* page 10, line 1) and that said combinations are suitable for treatment of asthma and/or COPD (*see* page 9, lines 21-22). The reference teaches that the therapeutic agent particles are spray dried (*see* page 37, line 1) and have a tap density of less than 0.4 g/cm^3 (*see* paragraph spanning pages 7-8), a mass mean aerodynamic diameter of 5 microns or less (*see* page 20, lines 7-12) and a fine particle fraction of greater than 50% (*see* page 22, lines 16-18). Basu et al. teach particles of the active agent (in a single active agent formulation) comprise 5 to 10 weight percent of the formulation (*see* page

77, claim 12). The reference teaches 1 to 46 weight percent phospholipid in the formulation (*see* page 76, claim 1). Basu et al. teach the addition of a phospholipid and leucine produces a sustained effect of the active agent (*see* page 5, lines 12-15).

Although Basu et al. do not teach *per se* the duration therapeutic efficacy as disclosed in the instant invention, absent evidence to the contrary, a formulation containing trospium, prepared by the methods of Basu et al. which anticipate the instant formulation methods, will have the same duration of therapeutic efficacy. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

The teachings of Basu et al. anticipate instant Claims 1, 2, 5-8, 10-13, 15, 22-24, and 26-28 and are thus properly rejected under 35 U.S.C. 102(a).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al. (U.S. Patent Application Pub. Number 2001/0008632), in view of Richards et al. (U.S. Patent Application Pub. Number 2003/0158176).

Freund et al. teach aqueous aerosols of *inter alia* trospium chloride (*see* page 2, paragraph 23) for inhalation in the treatment of respiratory passage diseases (*see* page 3, claim 2). Freund et al. also teach an active agent concentration range of 10mg/100ml to 20000mg/100ml and a nebuliser delivering 12 microliters of concentrate per operation (*see* page 3, paragraph 52). Therefore, the dose of active agent would be between 12 mcg and 2400 mcg per operation.

Freund et al. does not teach specific respiratory passage diseases or a specific dose for trospium.

Richards et al. teach anticholinergic (antimuscarinic) agents, including the quaternary ammonium compound, trospium, are useful for the treatment of acetylcholine-mediated disorders, in particular, the treatment of *inter alia* chronic obstructive pulmonary disease (COPD) and asthma (*see* page 5, paragraphs 91 and 93). Richards et al. teach the advantageous administration of these agents by inhalation or insufflation (*see* page 6, paragraph 103). Richards et al. teach that dose depends on many factors, including the potency of the compound, the age and weight of the patient and the severity of the condition (*see* page 6, paragraph 105). One of ordinary skill in the art would have optimized the dose taught by Freund et al. to maximize the therapeutic effects and minimize the deleterious effects of the active agent.

One of ordinary skill in the art (e.g., a pulmonologist) would have found it obvious to combine these two teachings to treat diseases such as COPD and asthma by local (i.e., inhalation) administration of trospium. One would have been motivated to administer trospium via inhalation to avoid excessive systemic absorption of the anticholinergic agent and resulting undesirable systemic effects (e.g., tachycardia, mydriasis, etc.), and to improve upon the known methods of treatment for COPD and asthma.

15. Claims 1, 2, 4, 6-8, 10-16, and 18-28 rejected under 35 U.S.C. 103(a) as being unpatentable over Basu et al. (WO/2003/079885), in view of Richards et al. (U.S. Patent Application Pub. Number 2003/0158176).

The teachings of Basu et al. have been presented *supra*.

Basu et al. does not teach the specific dose of trospium (200 to 800 mcg.) recited by instant Claims 4 and 18 or the frequency of administration recited by instant Claim 21. The reference does not teach the minimum amount of leucine recited by instant Claims 14 and 16. Basu et al. does not teach the durations of effective therapy recited by instant Claims 19 and 20. Although Basu et al. teach the administration of trospium alone or in combination with a second active agent (e.g. formoterol), the therapeutic use of both agents, each administered individually is not specifically taught.

Some of the teachings of Richards et al. are presented *supra*. Richards et al. also teach that doses administered by dry powdered or metered dose inhalers are "preferably given as one or two puffs, preferably comprising the total daily dose" (i.e., one dose per day) and that the preferred dosage ranges from 1 to 1000 mcg (*see* page

6, paragraph 106, and paragraph 109). Richards et al. teach that dose depends on many factors, including the potency of the compound, the age and weight of the patient and the severity of the condition (*supra*). One of ordinary skill in the art would have optimized the dose taught by Richards et al. to maximize the therapeutic effects and minimize the deleterious effects of the active agent.

Likewise, one of ordinary skill in the art would have used the teaching of Basu et al., that the addition of a phospholipid and leucine produces a sustained effect of the active agent (*supra*), to optimize the therapeutic duration of the formulation (i.e., by optimizing the amounts of leucine and a phospholipid in the formulation taught by Basu et al. to obtain the optimal therapeutic duration). One of ordinary skill would have recognized that the individual administration of two therapeutic agents provides the benefit of optimizing the dose of each agent for maximal therapeutic benefit, whereas the co-administration of both agents provides the benefit of simplifying the administration of the agents as well as improving patient compliance.

One of ordinary skill in the art, at the time of the invention, would have recognized the desirability of dry powder co-administration of the therapeutic agents, trospium and formoterol, for the treatment of restrictive respiratory diseases, such as COPD and asthma, and combined the teachings of Basu et al. with those of Richards et al. to produce a therapeutic agent with improved delivery and prolonged therapeutic effects. One would have been motivated to do so to improve upon the known methods of treatment for these respiratory diseases.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

16. Claims 1, 2, 4-8, 10-16, and 18-28 are rejected.

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on Mon-Thur 8:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gregg Polansky

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

10/9/07